What Are the Physiological Mechanisms by Which PM Causes Adverse Cardiac Effects?

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research and development

Introduction

- Epidemiological studies have reported a positive association between PM and the incidence of cardiovascular related morbidity and mortality. The robust nature of these associations has been sustained across a wide range of international urban centers and air sheds, and appears to be strengthened when limited to persons with preexisting cardiovascular disease (CVD). There is often a short time lag between exposure to increased levels of PM and the development of adverse effects, and there is a general consensus that the excess mortality is not due to "harvesting".
- Nevertheless, the underlying mechanisms of this response are still unknown. Given that CVD is the most prevalent cause of morbidity and mortality in the United States, impacting approximately 50% of the population, the likely potentiation of the effects of this disease with exposure to PM represents a major public health concern.
- Three potential pathways (see chart to left) have been proposed to explain how PM that enters the body through the lung may exert its primary impact on the cardiovascular system. Human and animal studies conducted to elucidate the mechanisms responsible for these effects have largely supported these proposed pathways.

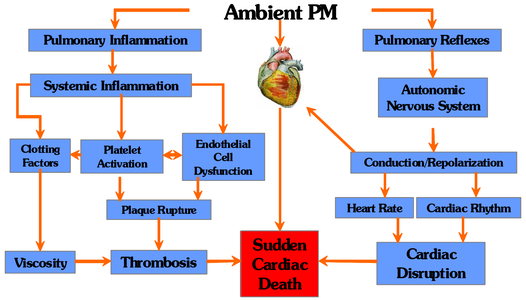
Research Goals

- examine the effects of exposures to particulate matter on cardiac (and pulmonary) indices in humans and animals
- elucidate plausible biological mechanisms responsible for these effects
- incorporate these mechanistic responses into logical scenarios that support and explain the epidemiological data

The poster presented by Cascio describes cardiovascular effects induced by PM in the elderly.

Methods/Approach

Potential Pathways for PM-Induced Cardiovascular Effects



Comparisons Between Experimental Approaches Used in Animal and Human Studies

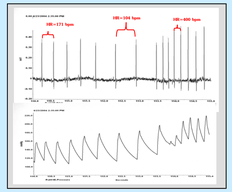
	Animal Studies	Human Studies*
Exposure Regimens	• instillation • nose-only inhalation • whole-body inhalation	• instillation • whole-body inhalation
Particulate Species	• combustion particles • metals/constituents • ambient particles • with/without gases	• combustion particles • metals/constituents • ambient particles • with/without gases
Animal Model/Disease	• pulmonary inflammation • pulmonary hypertension • COPD • systemic hypertension • myocardial ischemia • myocardial infarction • cardiomyopathy • old age	• asthma • cigarette smoke • diabetes • COPD • cardiac disease • ventricular fibrillation • myocardial ischemia • old age, children
Endpoints	• heart rate • blood pressure • arrhythmias • electrocardiograms • heart rate variability • blood biomarkers • cardiac pathology	• heart rate • blood pressure • arrhythmias • electrocardiograms • heart rate variability • blood biomarkers

Cardiac Effects – Animals

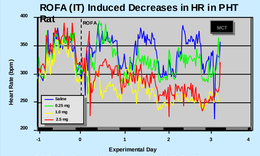
Heart Rate and Cardiac Function

Exposures to various species of PM have been shown to produce substantial changes in indices of cardiac function, e.g., heart rate, blood pressure, contractility, etc. Such changes in cardiac function can produce adverse effects, including lethality, in susceptible individuals.

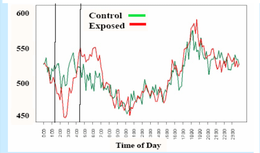
Ambient PM (IT) Induced Arrhythmias in SH Rat



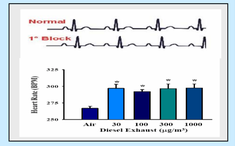
ROFA (IT) Induced Decreases in HR in PHT Rat



CAPs Induced Decreases in HR in Mouse

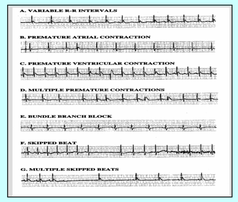


Diesel Increases PR-Interval and HR in Rat

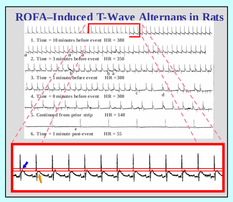


Electrocardiogram and Cardiac Rhythm

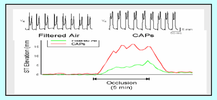
ROFA (IT) Induced Arrhythmias in PHT Rat



Metals (IT) Induced Arrhythmias/Lethality in PHT Rat

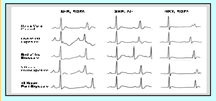


CAPs Induced ST-Segment Elevation in Dog



Both instilled and inhaled exposures to PM have also been shown to produce serious arrhythmias in rodents and dogs. Similar arrhythmias in humans are associated with life-threatening events.

ROFA Induced ST-Segment Depression in SH Rat

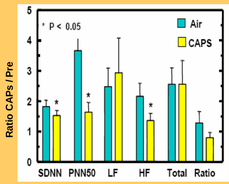


Cardiac Effects – Humans

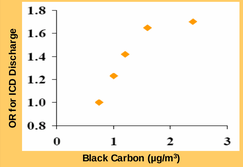
Cardiac Function and Rhythm

Corroborating studies in humans exposed to PM have demonstrated changes in both cardiac function and rhythm, similar to those seen in animal studies. Individuals with cardiopulmonary disease appear to be especially at risk.

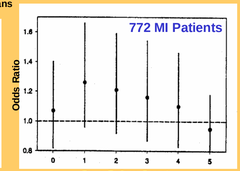
CAPs Induced Decreases in HRV in Humans



PM-Associated Increases in Arrhythmias in Humans



PM-Associated Increases in MI in Humans

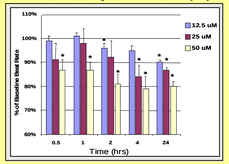


Cardiac Effects – Cellular

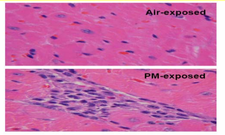
Cardiac Function and Injury

Direct effects on cellular parameters have been demonstrated following both *in vivo* and *in vitro* exposures to PM.

Zinc Decreases Beating Rate in Cardiac Myocytes



Zinc Increases Cellular Injury in Rat Hearts



These adverse effects range from functional to pathological and support both animal and human studies.

Results/Conclusions

- In addition to evidence of increased lethality in animals, these data demonstrate alterations in indices of cardiac function (e.g., heart rate, blood pressure, contractility), decreases in heart rate variability, and increases in arrhythmogenesis.
- The observed changes in cardiac function, heart rate variability, and electrocardiographic indices may serve as biomarkers for cardiac morbidity and mortality, especially in susceptible individuals.
- These studies generally support the observations of the epidemiological studies and implicate an important role for induced cardiac toxicity in PM-associated morbidity/mortality.

Future Directions

- Develop, characterize, and test new animal models of susceptibility and/or cardiopulmonary disease.
- Expose these new animal models to representative urban PM using "real world" exposure scenarios.
- Continue to develop and improve specific cardiovascular methodologies (e.g., ECG interval and heart rate variability analyses) and statistical approaches for application to rodent models.
- Strengthen and improve linkages between human and epidemiological studies and animal work to promote resolution of mechanistic pathways

Impact and Outcomes

- The elucidation of the underlying physiological mechanisms responsible for the induction of adverse cardiac effects following exposure to PM is crucial for the validation and interpretation of the epidemiological observations
- The demonstration of complimentary and corroborating data from both human and animal studies represents a critically important step in this effort
- The ultimate determination of these mechanisms will improve the ability to predict the likely toxicity of specific PM, constitutive agents, or output sources
- The subsequent establishment of linkages between toxicity and output sources will enhance and improve the specificity of the standard-setting process, provide crucial support for the mandated establishment of regulatory guidelines for PM by the USEPA, and thus lead to substantial improvements in public health

Health and Exposure